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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,568	02/17/2006	Michael Betz	BPG-32575A/BCK	5276
72554	7590	12/05/2008		
SANDOZ INC 506 CARNEGIE CENTER PRINCETON, NJ 08540				
EXAMINER				
STOICA, ELLY GERALD				
ART UNIT		PAPER NUMBER		
1647				
MAIL DATE		DELIVERY MODE		
12/05/2008		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/520,568

**Applicant(s)**

BETZ ET AL.

**Examiner**

ELLY-GERALD STOICA

**Art Unit**

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 5-8, 12, 13, 15, 18, 21-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-8, 12, 13, 15, 18, 21-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

***Status of the claims***

1. In the reply filed on 09/05/2008 Applicant amended claim 21. Claims 1-3, 5-8, 12, 13, 15, 18 and 21- 29 are pending and being examined.

***Withdrawn claim rejections***

***Claim Rejections - 35 USC § 112***

2. The rejection of claims 1-3, 5-8, 12, 13, 15, 18 and 21- 29 under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. (U.S. Pat. No. 5,763,394) in view of Asgharian B. (WO/99/06023, 11-1999) is withdrawn in view of the argument that Asgharian is not teaching injectable compositions.
3. The rejection of claims 1-3, 5-8, 12, 13, 15, 18 and 21- 29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the arguments and amendments to the claim 21.

***New Claim rejections***

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5-8, 12, 13, 15, 18 and 21- 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. (5,763,394) in view of Asgharian B. (WO/99/06023, 11-1999) and Fuentes V.M. ( U.S. Pat. No. 5,747,462).

The claims are drawn to a multi-dosage liquid pharmaceutical formulation of human growth hormone (hGH) consisting essentially of:

- a) about 5 mg/ml to about 100 mg/ml hGH,
- b) 1, 2-propylene glycol 0.5mg/ml to about 20 mg/ml
- c) an aqueous buffer,
- d) a non-ionic surfactant, and
- e) a preservative,

wherein the formulation has a tonicity of from about 100 mOsm/kg to about 500 mOsm/kg, pH of from about 6.1 to about 6.3. Preferably, the aqueous buffer is a phosphate, citrate, acetate, or formate buffer and the non-ionic surfactant is poloxamer 188 or a polysorbate at about 0.05 to about 4 mg/ml. Most preferably, the aqueous buffer is a phosphate buffer and the non-ionic surfactant is poloxamer 188. The tonicity-adjusting agent is selected from the group consisting of sugar, a sugar alcohol, a polyol

a neutral salt, and an amino acid, preferably mannitol. The preservative is selected from a group consisting of benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, phenol, benzalkonium chloride, benzethonium chloride, chlorobutanol, 2-phenoxyethanol, phenyl mercuric nitrate and thimerosal. The formulation is substantially isotonic and has a pH of about 6.2.

O'Connor et al. teach a stable pharmaceutically acceptable aqueous formulation containing human growth hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or a preservative. Also disclosed are associated means and methods for preparing, storing, and using such formulations (abstract).

Also disclosed by O'Connor is a human growth hormone formulation consisting of (claim 9):

- a) 1mg/ml to 20 mg/ml hGH,
- b) a preservative,
- c) a buffer system to provide a pH of 5.5 to 7,
- d) 0.1% w/v to 1% w/v non-ionic surfactant, and
- e) 50 mM to 200 mM neutral salt

O'Connor et al. further disclose the buffer is selected from the group consisting of citrate, phosphate and acetate buffers (claim 16) ) which are all aqueous buffers, and is most advantageously in the range of about 2 mM to about 50 mM (column 3, lines 46-48). O'Connor et al. further disclose the non-ionic surfactant is poloxamer 188, poloxamer 184, or polysorbate (claims 11 and 12) in a concentration range of 0.1% to 5% (w/v), which is 1-50 mg/ml. (col. 3, lines 35-39). O'Connor et al. further disclose

preservatives like phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalconium chloride, and benzethonium chloride (column 3, lines 50-54). O'Connor et al. further disclose that about 5 mg/ml to about 50 mg/ml mannitol may be included in the aqueous hGH formulations, as opposed to the neutral salts (column 3, lines 62-64). O'Connor et al. further disclose a directly injectable hGH formulation consisting essentially of: a) 5mg/ml hGH, b) 0.5 mg/ml phenol, c) 2.5 mg/ml sodium citrate (aqueous buffer), d) 2.0 mg/ml polysorbate 20 (non-ionic surfactant), and e) 8.8 mg/ml sodium chloride (neutral salt/tonicity agent) wherein the hGH formulation is at a pH of 6 (claim 18) and the buffer concentration range is chosen to minimize deamidation, aggregation and precipitation of hGH (col. 3, lines 59-61). O'Connor et al. further disclose that the formulation is adjusted to near isotonicity with saline solutions, depending on the other ingredients present in the formulation (column 4, lines 1-5). The osmolarity is an inherent property to the tonicity adjusting reagents. As disclosed by O'Connor, the concentration range of the hGH in the formulation is not critical and may be varied by the clinician administering the drug (col. 3, line 19-25). O'Connor et al are silent about specifically using 1, 2-propylene glycol in their formulations even though they mention using polyols in their formulations.

Asgharian teaches topical ophthalmic compositions which provide controlled administration of a drug to the eye (p.3, lines 14-16). Further, the pharmaceutical compositions include tonicity agents such as salts (sodium chloride, potassium chloride and calcium chloride) or non- ionic tonicity agents such as propylene glycol (p. 10, lines 3-7). In Example 4, the amount of propylene glycol used is 14 mg/ml.

Fuentes teaches pharmaceutically active compounds for treating inflammation, pain, pruritus and local hyperthermia in human beings and animal species (abstract). For parenteral administration a wide variety of liquid formulations, such as injectable sterile solutions, utilize inert diluents such as propylene glycol (col. 14, lines 1-9).

As presented supra, O'Connor et al. teach all the basic limitations of claims, less the specific use of propylene glycol either for tonicity purposes or other purposes. Asgharian specifically teaches the use of propylene glycol for tonicity adjustment or other purposes (offering even a concentration that is in the range claimed in the instant Application). It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the teachings of O'Connor et al., combined with the teachings of Asgharian to obtain the formulations of the instant Application, with a reasonable expectation of success. That is because O'Connor teaches the elements and the ranges of the hGH formulations and Asgharian singles out the use of 1, 2 propylene glycol for tonicity adjustment and it was known in the art that injectable formulations may contain propylene glycol, as evidenced by Fuentes et al. The optimization of pH and tonicity values is routine in the art for pharmaceutical formulation as suggested also by O'Connor. Even though Asgharian does not teach injectable formulations containing propylene glycol, Fuentes specifically mentions the propylene glycol for injectable formulations of pharmaceutical compounds. Thus, by following these teachings the skilled artisan would have applied the existent knowledge in the art. It is also worth considering that: "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re

Boesch, 617 F.2d 272,276, 205 USPQ 215, 219 (CCPA 1980). See also *Merck & Co. v. Biocraft Labs. Inc.*, 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989). In this case it is not a process but a composition, but the rationale set forth in *Boesch* clearly applies.

Relevant in this situation is the fact that obviousness does NOT require the reference to teach every limitation of the claim. A reference renders claims obvious if it discloses the claimed invention "such that a skilled artisan could take its teachings in combined with his own knowledge of the particular art and be in possession of the invention". In *re Graves*, 36 USPQ 2d1697 at 1701

On page 9 of the Remarks Applicant argues that the teachings of O'Connor et al. and Asgharian are from non-analogous art and that Asgharian teaches gel-formulations while O'Connor and the instant Application are directed to injectable formulations. The arguments were carefully considered but not found persuasive because, in response to applicant's argument that Asgharian is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Asgharian presents a pharmaceutical formulation that contains propylene glycol and offers the reason to use the propylene glycol: tonicity adjusting agent. The composition of Asgharian does not become a gel because propylene glycol is used. That is even more underscored by Fuentes which uses propylene glycol in the injectable formulations.



Therefore, when read comprehensively, the three references contain all the elements of the instant claims and a person of ordinary skill in the art would not have had any hesitation to use the references to make the compositions of the instant Application with an excellent expectation of success, since he or she would have applied routine knowledge existent in the art at the time that the invention was made.

### ***Conclusion***

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic

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Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/

Primary Examiner, Art Unit 1647